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(54) Title: DELIVERY OF THERAPEUTIC CAPABLE AGENTS

(57) Abstract: A device and a method using the same, for reducing restenosis and hyperplasia after intravascular intervention. In particular, the present invention provides luminal prostheses which allow for controlled release of at least one therapeutic capable agent with increased efficacy to selected locations within a patient's vasculature to reduce restenosis. An intraluminal prosthesis may comprise an expandable structure and a source adjacent the expandable structure for releasing the therapeutic capable agent into the body lumen to reduce smooth muscle cell proliferation.

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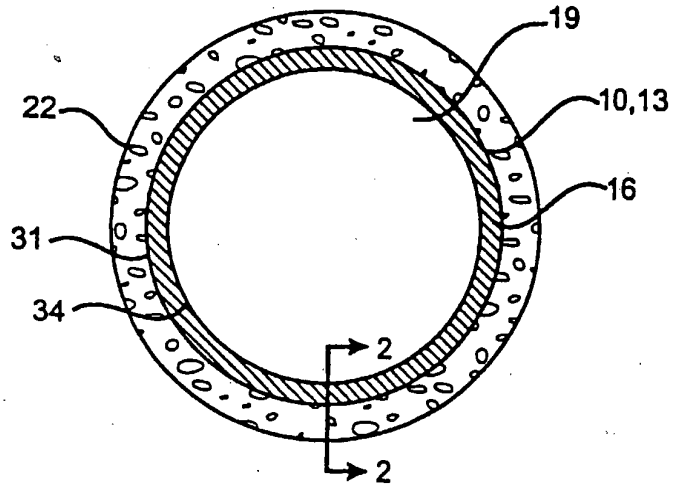
(54) Title: DELIVERY OF THERAPEUTIC CAPABLE AGENTS



(57) Abstract: A device and a method using the same, for reducing restenosis and hyperplasia after intravascular intervention. In particular, the present invention provides luminal prostheses which allow for controlled release of at least one therapeutic capable agent with increased efficacy to selected locations within a patient's vasculature to reduce restenosis. An intraluminal prosthesis may comprise an expandable structure and a source adjacent the expandable structure for releasing the therapeutic capable agent into the body lumen to reduce smooth muscle cell proliferation.

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entirely successful in substantially or completely avoiding all occurrences of restenosis and hyperplasia.

[06] As an alternative or adjunctive to the above mentioned therapies, the administration of therapeutic agents following PTA for the inhibition of restenosis has also been proposed. Therapeutic treatments usually entail pushing or releasing a drug through a catheter or from a stent. While holding great promise, the delivery of therapeutic agents for the inhibition of restenosis has not been entirely successful.

[07] Accordingly, it would be a significant advance to provide improved devices and methods for reducing, inhibiting, or treating restenosis and hyperplasia which may follow angioplasty and other interventional treatments. This invention satisfies at least some of these and other needs.

[08] 2. Description of the Background Art

[09] A full description of an exemplary luminal prosthesis for use in the present invention is described in co-pending application No. 09/565,560 filed May 4, 2000, the full disclosure of which is incorporated herein by reference. Method and apparatus for releasing active substances from implantable and other devices are described in U.S. Patent Nos. 6,096,070; 5,824,049; 5,624,411; 5,609,629; 5,569,463; 5,447,724; and 5,464,650. The use of stents for drug delivery within the vasculature are described in PCT Publication No. WO 01/01957 and U.S. Patent Nos. 6,099,561; 6,071,305; 6,063,101; 5,997,468; 5,980,551; 5,980,566; 5,972,027; 5,968,092; 5,951,586; 5,893,840; 5,891,108; 5,851,231; 5,843,172; 5,837,008; 5,769,883; 5,735,811; 5,700,286; 5,679,400; 5,649,977; 5,637, 113; 5,591,227; 5,551,954; 5,545,208; 5,500,013; 5,464,450; 5,419,760; 5,411,550; 5,342,348; 5,286,254; and 5,163,952. Biodegradable materials are described in U.S. Patent Nos. 6,051,276; 5,879,808; 5,876,452; 5,656,297; 5,543,158; 5,484,584; 5,176,907; 4,894,231; 4,897,268; 4,883,666; 4,832,686; and 3,976,071. The use of hydrocyclosiloxane as a rate limiting barrier is described in U.S. Patent No. 5,463,010. Methods for coating of stents is described in U.S. Patent No. 5,356,433. Coatings to enhance biocompatibility of implantable devices are described in U.S. Patent Nos. 5,463,010; 5,112,457; and 5,067,491. Energy based devices are described in U.S. Patent Nos. 6,031,375; 5,928,145; 5,735,811; 5,728,062; 5,725,494; 5,409,000, 5,368,557; 5,000,185; and 4,936,281. Magnetic processes, some of which have been used in drug delivery systems, are described in U.S. Patent Nos. 5,427,767; 5,225,282; 5,206,159; 5,069,216; 4,904,479; 4,871,716; 4,501,726; 4,357,259; 4,345,588; and 4,335,094.

including coronary and peripheral arteries, as well as previously implanted grafts, shunts, fistulas, and the like. It will be appreciated that the present invention may also be applied to other body lumens as well as to many internal corporeal tissue organs, such as organs, nerves, glands, ducts, and the like. An exemplary stent for use in the present invention is described in co-pending application No. 09/565,560.

[15] It will be appreciated that the above-described benefits of time delayed release allow for a wide array of substances to be effectively delivered. The substance may comprise at least one agent selected from the group consisting of immunosuppressant agent, anti-inflammatory agent, anti-proliferative agent, anti-migratory agent, anti-fibrotic agent, anti-thrombotic agent, anti-platelet agent, and IIb/IIIa agent. Preferably, the agent is an immunosuppressant agent selected from the group consisting of mycophenolic acid, rapamyacin, cyclosporine A, cycloheximide, cyclophosphamide, mizoribine, methylprednisolone, azathioprine, ribovirin, FK506, tiazofurin, methotrexate, zafurin, and mycophenolate mofetil. The total amount of substance released will typically be in a range from 1 g. to 2000 g., preferably in a range from 10 g. to 1000 g., most preferably in a range from 50 g. to 500 g. The release rate during the initial phase will typically be from 0 g/day to 50 g/day, usually from 5 g/day to 30 g/day. The substance release rate during the subsequent phase will be much higher, typically being in the range from 5 g/day to 200 g/day, usually from 10 g/day to 100 g/day. Thus, the initial release rate will typically be from 0 % to 99 % of the subsequent release rates, usually from 0 % to 90 %, preferably from 0 % to 75 %. Of course, the release rates may vary during either or both of the initial and subsequent release phases. There may also be additional phase(s) for release of the same substance(s) and/or different substance(s).

[16] The duration of the initial, subsequent, and any other additional phases may vary. Typically, the initial phase will be sufficiently long to allow initial cellularization or endothelialization of at least part of the stent, usually being less than 12 weeks, more usually from 1 hour to 8 weeks, more preferably from 12 hours to 2 weeks, most preferably from 1 day to 1 week. The durations of the subsequent phases may also vary, typically being from 4 hours to 24 weeks, more usually from 1 day to 12 weeks, more preferably in a time period of 2 days to 8 weeks in a vascular environment, most preferably in a time period of 3 days to 50 days in a vascular environment.

[17] The present invention is directed to improved devices and methods for preparation or treatment of susceptible tissue sites. As used herein, susceptible tissue site refers to a tissue site that is injured, or may become injured as a result of an impairment (e.g., disease, medical

substantially constant size or diameter, or alternatively depending on the application and use, may be a contractable structure. In an embodiment, the structure includes at least one surface, usually, a tissue facing surface. In another embodiment, the structure includes a tissue facing surface and another surface, usually a lumen facing surface. In an embodiment, the structure may have an interior disposed between two surfaces, usually, the tissue facing and the lumen facing surfaces.

[21] The device may include an expandable structure implantable within a corporeal body which includes the susceptible tissue site. The device, alternatively or additionally, may be an implantable device configured for implanting with or without expansion at a targeted corporeal site. The targeted corporeal site may include the susceptible tissue site or may be a site (e.g., other body organs or lumens), for example a targeted intracorporeal site such as an artery, which supplies blood to the susceptible tissue site. In an embodiment, the expandable structure may be in the form of a stent, which additionally maintains luminal patency, or in the form of a graft, which additionally protects or enhances the strength of a luminal wall. The device, may comprise at least in part, a scaffold formed from an open lattice or an at least substantially closed surface. In an embodiment, the stent comprises a scaffold formed at least in part from an open lattice. The expandable structure may be radially expandable and/or self-expanding and is preferably suitable for luminal placement in a body lumen.

[22] The expandable structure may be formed of any suitable material such as metals, polymers, or a combination thereof. In one embodiment, the expandable structure may be formed of an at least partially biodegradable material, selected from the group consisting of polymeric material, metallic materials, or combinations thereof. The at least partially biodegradable material, preferably degrades over time. Examples of polymeric material include poly-L-lactic acid, having a delayed degradation to allow for the recovery of the vessel before the structure is degraded. Example of metallic material include metals or alloys degradable in the corporeal body, such as stainless steel. An exemplary stent for use in the present invention is described in co-pending application No. 09/565,560, the full disclosure of which is incorporated herein by reference.

[23] The therapeutic capable agent is associated at least in part with the structure in a manner as to become available, immediately or after a delay period, to the susceptible tissue site upon introduction of the device within or on the corporeal body. As used herein the term "associated with" refers to any form of association such as directly or indirectly being coupled to, connected to, disposed on, disposed within, attached to, adhered to, bonded to, adjacent to, entrapped in, absorbed in, absorbed on, and like configurations.

converts within the body directly or upon introduction of other agents or conditions (e.g., enzymatic, chemical, energy), or environment (e.g., pH)).

[28] The therapeutic capable agent may be selected from a group consisting of immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents, proapoptotics, calcium channel blockers, anti-neoplastics, antibodies, anti-thrombotic agents, anti-platelet agents, IIb/IIIa agents, antiviral agents, and a combination thereof.

[29] Specific examples of therapeutic capable agent include: mycophenolic acid, mycophenolate mofetil, mizoribine, methylprednisolone, dexamethasone, Certican™, rapamycin, Triptolide™, Methotrexate™, Benidipine™, Ascomycin™, Wortmannin™, LY294002, Camptothecin™, Topotecan™, hydroxyurea, Tacrolimus™ (FK 506), cyclophosphamide, cyclosporine, daclizumab, azathioprine, prednisone, Gemcitabine™, derivatives and combinations thereof.

[30] In an embodiment, the source of the therapeutic capable agent is a polymeric material including therapeutic capable agent moieties as a structural subunit of the polymer. The therapeutic capable agent moieties are polymerized and associated to one another through suitable linkages (e.g. ethylenic) forming polymeric therapeutic capable agent. Once the polymeric therapeutic capable agent is brought into contact with tissue or fluid such as blood, the polymeric therapeutic capable agent subunits disassociate. Alternatively, the therapeutic capable agent may be released as the polymeric therapeutic capable agent degrades or hydrolyzes, preferably, through surface degradation or hydrolysis, making the therapeutic capable agent available to the susceptible tissue site, preferably over a period of time. Examples of methods and compounds for polymerizing therapeutic capable agents are described in WO 99/12990 Patent Application by Kathryn Uhrich, entitled "Polyanhydrides With Therapeutically Useful Degradation Products," and assigned to Rutgers University, the full disclosure of which is incorporated herein by reference. An example of a therapeutic capable agents and a suitable reaction ingredient unit includes, mycophenolic acid with adipic acid and/or salicylic acid in acid catalyzed esterification reaction; mycophenolic acid with aspirin and/or adipic acid in acid catalyzed esterification reaction, mycophenolic acid with other NSAIDS, and/or adipic acid in acid catalyzed esterification reaction. In an embodiment, the polymeric therapeutic capable agent may be associated with a polymeric and/or metallic backbone.

embodiment a mammalian tissue concentration of the substance at an initial phase will typically be within a range from about 0.001 nanogram (ng)/mg of tissue to about 100 ug/mg of tissue; from about 1 ng/mg of tissue to about 100 ug/mg of tissue; from about 1 ng/mg of tissue to about 10 ug/mg of tissue. A mammalian tissue concentration of the substance at a subsequent phase will typically be within a range from about 0.001 ng/mg of tissue to about 600 ug/mg of tissue, preferably from about 1 ng/mg of tissue to about 10 ug/mg of tissue.

[37] The rate of delivery during the initial phase will typically range from about 0.001 ng to about 50 ug per day, usually from about 0.1 ug to about 30 ug per day, more preferably, from about 1 ug per day to about 20 ug per day. The rate of delivery at the subsequent phase may range from about 0.01 ug per day to about 200 ug per day, usually from about 1ug per day to about 100 ug per day. In one embodiment, the therapeutic capable agent is made available to the susceptible tissue site in a programmed and/or controlled manner with increased efficiency and/or efficacy. Moreover, the present invention provides limited or reduced hindrance to endothelialization of the vessel wall.

[38] The duration of the initial, subsequent, and any other additional phases may vary. For example, the release of the therapeutic capable agent may be delayed from the initial implantation of the device. Typically the delay is sufficiently long to allow the generation of sufficient cellularization or endothelialization at the treated site to inhibit loss of the therapeutic capable agent into the vascular lumen.. Typically, the duration of the initial phase will be sufficiently long to allow initial cellularization or endothelialization at, at least part of the device. Typically, the duration of the initial phase whether being a delayed phase or a release phase, is usually less than about 12 weeks, more usually from about 1 hour to about 8 weeks, more preferably from about 12 hours to about 4 weeks, from about 12 hours to about 2 weeks, from about 1 day to about 2 weeks, or from about 1 day to about 1 week.

[39] The durations of the one or more subsequent phases may also vary, typically being from about 4 hours to about 24 weeks, from about 1 day to about 12 weeks, from about 2 days to about 8 weeks, more preferably in from about of 3 days to about 50 days. In an embodiment, the duration specified relates to a vascular environment. The more than one phase may include similar or different durations, amounts, and/or rates of release. For example, in one scenario, there may be an initial phase of delay, followed by a subsequent phase of release a first subsequent rate, and second subsequent phase at a second subsequent rate of release, and the like.

[40] In an embodiment, the device further includes another compound, such as another therapeutic capable agent, or another compound enabling and/or enhancing either or both the

[46] In an embodiment, the rate-controlling element may be disposed or formed adjacent the structure. In one embodiment, the rate-controlling element may be disposed or formed adjacent at least a portion of the optional one or more surfaces of the structure (e.g., luminal or tissue facing surfaces), or within the optional interior of the structure, or any combination thereof. The therapeutic capable agent or the optional another compound may be disposed adjacent the rate-controlling element. Additionally and/or alternatively, in one embodiment, the therapeutic capable agent or the optional another compound may be disposed within the rate-controlling element forming a matrix therewith. In an embodiment, the therapeutic capable agent or the optional another compound itself is a rate-controlling element, as for example, when the therapeutic capable agent or the optional another compound is a polymeric material.

[47] The term matrix as used herein refers to an association between the rate-controlling element and the therapeutic capable agent (or the optional another compound) and/or the therapeutic capable agent (or the optional another compound) and any other compounds or structures affecting the release of the therapeutic capable agent. In an embodiment, the matrix is formed as a matrix interface between the rate-controlling element and the therapeutic capable agent and/or the optional another compound. In an embodiment, the rate-controlling element may comprise multiple adjacent layers formed from the same or different material. The therapeutic capable agent or the optional another compound may be present adjacent one or more of the rate-controlling element layers. Additionally and/or alternatively, the therapeutic capable agent or the optional another compound may form a matrix and/or matrix interface with one or more of the rate-controlling element layers.

[48] In another embodiment, when the rate-controlling element is present as multiple layers, the any one of the more than one layers may include independently none, one, or more of the plurality of compounds (e.g., the at least one therapeutic capable agent, another compound. Each of the plurality of compounds such as the another compound and/or more than one therapeutic capable agent, may form a different matrix with the rate-controlling element. In an embodiment, as further described below, the therapeutic capable agent may form the matrix, as when the therapeutic capable agent is a polymeric therapeutic capable agent, thus controlling the release of the active component to the susceptible tissue site. Alternatively, or additionally, the rate-controlling element may be another compound, such as another therapeutic capable agent which can have an impact on the release rate of the first therapeutic capable agent.

silicone, polytetrafluoroethylene, parylast, polyurethane, parylene, cellulose acetate butyrate; mixtures, copolymers and combinations thereof.

[53] Suitable natural material include: fibrin, albumin, collagen, gelatin, glycosoaminoglycans, oligosaccharides & poly saccharides, chondroitin, phosholipids, phosphorylcholine, glycolipids, proteins, amino acids, cellulose, and mixtures, copolymers, or combinations thereof. Other suitable material include, titanium, chromium, Nitinol, gold, stainless steel, metal alloys, or a combination thereof; and other compounds that may release the therapeutic capable agent as a result of interaction (e.g., chemical reaction, high molecular weight, steric hindrance, hyrophobicity, hydrophilicity, amphilicity, heat) of the therapeutic capable agent with the rate-controlling element material (e.g, a non-polymer compound). By way of example, a combination of two or more metals or metal alloys with different galvanic potentials to accelerate corrosion by galvanic corrosion pathways may also be used.

[54] In another embodiment, the surface of the structure may be pre-processed using any of a variety of procedures, including, cleaning; physical modifications such as etching or abrasion; and chemical modifications such as solvent treatment, the application of primer coatings, the application of surfactants, plasma treatment, ion bombardment, and covalent bonding. In an embodiment, a metal film or alloy with a small pits or pin holes to accelerate corrosion by pitting corrosion, allowing the pin hole formed by the corrosion to act as an orifice for drug release. In an embodiment, the therapeutic capable agent may be attached to the metal or metal alloy.

[55] The degradable material may degrade by bulk degradation or hydrolysis. In an embodiment, the rate-controlling element degrades or hydrolyzes throughout, or preferably, by surface degradation or hydrolysis, in which a surface of the rate-controlling element degrades or hydrolyzes over time while maintaining bulk integrity. In another embodiment, hydrophobic rate-controlling elements are preferred as they tend to release therapeutic capable agent at desired release rate. A non-degradable rate-controlling element may release therapeutic capable agent by diffusion. By way of example, if the rate-controlling element is formed of non-polymeric material, the therapeutic capable agent may be released as a result of the interaction (e.g., chemical reaction, steric hinderence, hyrophobicity, hydrophilicity, amphilicity) of the therapeutic capable agent with the rate-controlling element material (e.g, a non-polymer compound). In an embodiment, when the rate-controlling element does not form, at least a sufficient matrix with the therapeutic capable agent, the therapeutic capable agent may be released by diffusion through the rate-controlling element.

released within a time period of 2 days to 3 months, from the time of interventional procedure.

[61] The devices of the present invention may be provided together with instructions for use (IFU), separately or as part of a kit. The kit may include a pouch or any other suitable package, such as a tray, box, tube, or the like, may be used to contain the device and the IFU, where the IFU may be printed on a separate sheet or other media of communication and/or on the packaging itself. In an embodiment of a kit, the kit may also include a mounting hook such as a crimping device and/or an expansible inflation member which may be permanently or releaseably coupled to the device of the present invention. In an embodiment, the kit may comprise the device and an IFU regarding the use of a second compound prior to, concurrent with, or subsequent to, the interventional procedure, and optionally the second compound. In an embodiment, the kit comprises the device and the second compound with or without the IFU for the second compound and/or the device.

[62] In one embodiment, the second compound, may be a therapeutic capable agent, an another compound (e.g., the another therapeutic capable agent and/or the another enabling and/or enhancing compound), or a bio-active compound such as an anti-nausea drug; and being similar or different than that made available to the susceptible tissue site by the device; may be administered prior to, concurrent with, or subsequent to the implanting of the device (e.g., prosthesis) of the present invention.

[63] The second compound may be administered from a pathway similar to or different than that used for the delivery of the therapeutic capable agent as part of the device. By way of example, the second compound may be in the form of a tablet to be taken orally, a transdermal patch to be placed on the patient's skin, subcutaneously, systemically by direct introduction to the blood stream, by way of inhalation, or through any other pathways and bodily orifices. Alternatively, the second compound may be made available to the intracorporeal body by a catheter. In an embodiment, the balloon of a balloon catheter (e.g., perfusion), may be used to perfuse the second compound (e.g., perfusion catheter) into the corporeal body or may be coated with the second compound. The second compound may be made available to the patient continuously or in discrete intervals, prior to, concurrent with, or subsequent to the interventional procedure.

[64] The duration of the availability of the second compound usually may be shorter as compared to that of the therapeutic capable agent. In an embodiment, the another compound may be administered to the patient in a time period ranging from about 200 days prior to about 200 days after the interventional procedure, from about 30 days prior to about 30 days

yet another embodiment, the release of the therapeutic capable agent may occur by bulk degradation of the source. In another embodiment, the releasing the therapeutic capable agent may occur by diffusion through the source. In an embodiment a device including a source of therapeutic capable agent and incorporating any one or more features of the present invention is delivered to a corporeal site such as an intracorporeal body (e.g., body lumen). The corporeal site may be a targeted corporeal site (such as a targeted intracorporeal site), which includes the susceptible tissue site, or a targeted site directly or indirectly providing the therapeutic capable agent to the susceptible tissue site. The therapeutic capable agent is made available to the susceptible tissue site, preferably, in a controlled manner over a period of time.

[67] Methods of treatment, generally, include positioning the source including the at least one therapeutic capable agent and/or optional another compound within the intracorporeal body, concurrently with, or subsequent to, an interventional treatment. More specifically, the therapeutic capable agent may be delivered to a targeted corporeal site (e.g., targeted intracorporeal site) which includes the susceptible tissue site or a targeted site providing the therapeutic capable agent to the susceptible tissue site, concurrently with or subsequent to the interventional treatment. By way of example, following the dilation of the stenotic region with a dilatation balloon, a device (such as a stent) according to the present invention, is delivered and implanted in the vessel. The therapeutic capable agent may be made available to the susceptible tissue site at amounts which may be sustainable, intermittent, or continuous; at one or more phases and/or rates of delivery.

[68] In an embodiment, the release of the therapeutic capable agent to the susceptible tissue site may be delayed. During the delay period none to small amounts of therapeutic capable agent may be released before the release of substantial amount of therapeutic capable agent. Typically the delay is sufficiently long to allow the sufficient generation of intimal tissue or cellularization, at the treated site to reduce occurrence of thrombotic event.

[69] In one embodiment, delay is sufficiently long to allow the generated neointima to cover at least partially the implanted expandable structure. In an embodiment, the therapeutic capable agent may be released in a time period, as measured from the time of implanting of the device, ranging from about 1 day to about 200 days; from about 1 day to about 45 days; or from about 7 days to about 21 days. In an embodiment, the method further includes directing energy at the device to effect release of the therapeutic capable agent from the device. The energy may include one or more of ultrasound, magnetic resonance imaging, magnetic field, radio frequency, temperature change, electromagnetic, x-ray, heat, vibration,

including a therapeutic capable agent 28. The device 10, as shown, is disposed in the body lumen 19. It should be appreciated, that although the source 25 as depicted in the figures is disposed adjacent a surface of the expandable structure, the word adjacent is not intended to be limited by the exemplary figures or descriptions.

[80] The expandable structure may be formed of any suitable material such as metals, polymers, or a combination thereof. In one embodiment, the expandable structure may be formed of an at least partially biodegradable material, selected from the group consisting of polymeric material, metallic materials, or combinations thereof. The at least partially biodegradable material, preferably degrades over time. Examples of polymeric material include poly-L-lactic acid, having a delayed degradation to allow for the recovery of the vessel before the structure is degraded. Example of metallic material include metals or alloys degradable in the corporeal body, such as stainless steel. An exemplary stent for use in the present invention is described in co-pending application No. 09/565,560, the full disclosure of which is incorporated herein by reference.

[81] As used herein therapeutic capable agent includes at least one compound which is either therapeutic as it is introduced to the corporeal body (e.g., human subject) under treatment, or becomes therapeutic after entering the corporeal body of the subject (or exposed to the surface of the corporeal body as the case may be), by for example, reaction with a native or non-native substance or condition. Examples of native conditions include pH (e.g. acidity), chemicals, temperature, salinity, and conductivity; with non-native conditions including those such as magnetic fields, and ultrasound. In the present application, the chemical name of any of the therapeutic capable agents or other compounds is used to refer to the compound itself and to pro-drugs (precursor substances that are converted into an active form of the compound in the body), and/or pharmaceutical derivatives, analogues, or metabolites thereof (bioactive compound to which the compound converts within the body directly or upon introduction of other agents or conditions (e.g., enzymatic, chemical, energy), or environment (e.g., pH)).

[82] The therapeutic capable agent may be selected from a group consisting of immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents, proapoptotics, calcium channel blockers, anti-neoplastics, antibodies, anti-thrombotic agents, anti-platelet agents, IIb/IIIa agents, antiviral agents, and a combination thereof.

cause the cells to accumulate in the G1-S phase of the cell cycle and thus result in inhibition of DNA synthesis and cell proliferation (hyperplasia).

[87] Methylprednisolone is a synthetic steroid in the class of glucocorticoids that suppresses acute and chronic inflammations. In addition, it reduced vascular smooth muscle generation. Its anti-inflammatory actions include inhibition of accumulation of inflammatory cells (including macrophages and leukocytes) at inflammation sites, and inhibition of phagocytosis, lysosomal enzyme release, and synthesis and/or release of several chemical mediators; immunosuppressant actions may involve prevention/suppression of cell-mediated (delayed hypersensitivity) immune reactions and more specific actions affecting immune response; immunosuppressant actions may also contribute significantly to the anti-inflammatory effect.

[88] Certican™, also known as everolimus, SDZ-RAD, RAD, RAD666, or 40-0-(2-hydroxy)ethyl-rapamycin, is a potent immunosuppressant and anti-inflammatory agent. In particular, Certican™ acts to inhibit the activation and proliferation of T lymphocytes in response to stimulation by antigens, cytokines (IL-2, IL-4, and IL-15), and other growth-promoting lymphokines. Certican™ also inhibits antibody production. In cells, Certican™ binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The Certican:FKBP-12 complex, which has no effect on calcineurin activity, binds to and inhibits the activation of the mTOR, a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression of the cell cycle from the G1 to the S phase, selectively blocking signals leading to the activation of p70s6k, p33cdk2 and p34cdc2. Thus, Certican™ administration results in inhibiting proliferation of T and B cells, inflammatory cells, as well as smooth muscle cells (hyperplasia).

[89] Triptolide™ or related compounds, such as, tripdiolide, diterpenes, triterpenes, diterpene epoxides, diterpenoid epoxide, triepoxides, or tripterygium wifordii hook F (TWHF), are also potent immunosuppressant and anti-inflammatory agents. Specifically, Triptolide™ has been shown to inhibit the expression of IL-2 in activated T cells at the level of purine-box/nuclear factor and NF-kappaB mediated transcription activation. Triptolide™ may induce apoptosis in tumor cells and potentiate a tumor necrosis factor (TNF-alpFha) induction of apoptosis in part through the suppression of c-IAP2and c-IAP1 induction. Triptolide™ inhibits the transcriptional activation, but not the DNA binding, of nuclear factor-kappaB. Triptolide™ may also inhibit expression of the PMA-induced genes tumor necrosis factor-alpha, IL-8, macrophage inflammatory protein- 2alpha, intercellular adhesion molecule-1, integrin beta6, vascular endothelial growth factor, granulocyte macrophage

and reperfusion injury. Since myocardial ischemia impairs endothelial cell function by the activation of platelets and leukocytes, benidipine may attenuate endothelial cell dysfunction and increase the production of nitric oxide in ischemic hearts.

[93] Ascomycin (molecular formula: $C_{43}H_{69}NO_{12}$; molecular weight: 792.02; CAS No. 104987-12-4) has produced significant anti-inflammatory and immunosuppressant activity. Ascomycin has been shown to selectively inhibit inflammatory cytokine release. The drug binds to the cytosolic immunophilin receptor macrophilin-12, and the resulting complex inhibits the phosphatase calcineurin, thus blocking T-cell activation and cytokine release. It inhibits production of Th1 cytokines (interleukin-2 and interferon-gamma) and Th2 cytokines (interleukin-10 and interleukin-4). Ascomycin has also been demonstrated to similarly inhibit mast cell. Strong immunosuppressant; inhibits allogenic T-lymphocyte proliferation. It binds with high affinity to FKBP and inhibits calcineurin phosphatase in the nM range.

[94] Ascomycin affects calcineurin-mediated signal transduction. It is a natural product of bacteria and fungi, respectively, with potent immunosuppressive, anti-inflammatory, and antimicrobial activity. Despite differing chemical structures, ascomycin is a macrolide where its mechanisms of action and cellular effects results in the inhibition of the protein phosphatase calcineurin. This drug is hydrophobic and thought to diffuse across the plasma membrane; once inside the cell, Ascomycin forms complexes with their major receptors, FKBP12. FKBP12 is small, ubiquitous, cytosolic proteins that catalyse *cis–trans* prolyl isomerization, a reaction that can be a rate-limiting step in protein folding. Binding of ascomycin to FKBP12 inhibits prolyl-isomerase activity. However, this inhibition is not the major toxic effect in the cell; instead the FKBP12–ascomycin complex binds to and inhibit calcineurin (a serine–threonine-specific protein phosphatase), which is activated by calmodulin in response to intracellular calcium-ion increases. The molecular nature of this interaction is now known in considerable detail, as the structures of both calcineurin alone and in a ternary complex with FKBP12–ascomycin have both been solved at high resolution.

[95] Wortmannin (CAS No. 19545-26-7, synonym SL-2052, molecular formula: C23H24O8 formula weight: 428.4 (anhydrous)) has significant anti-inflammatory and immunosuppressant activity. Wortmannin, a fungal metabolite, is a specific and potent inhibitor of myosin light chain kinase and a potent inhibitor of neutrophil activation by inhibiting F-met-leu(FMLP)-phe-stimulated superoxide anion production without affecting intracellular calcium mobilization. It inhibits FMLP-stimulated phospholipase D activation without direct inhibition of the enzyme. It also inhibits phosphatidylinositol-3-kinase (PI3-

[99] LY294002 has produced significant anti-inflammatory and immunosuppressant activity. LY294002 has been used in some cases to confirm the effects of wortmannin attributed to inhibition of PI-3 kinase, but this compound also inhibits mTOR and may inhibit other wortmannin targets as well. Hence, more enzyme-specific analogues of wortmannin would be valuable reagents to probe the intracellular functions of this intriguing family of enzymes. The wortmannin analogue demethoxyviridin has been shown to inhibit an as-yet-unidentified PI-4-kinase activity in *Schizosaccharomyces pombe* that is much less sensitive to wortmannin, indicating that analogues with greater specificity may be obtained.

[100] Camptothecin and Topotecan (Hycamtin) - Camptothecin (molecular formula: $C_{20}H_{16}N_2O_4$, molecular weight: 348.4, CAS No. 7689-03-4) and its analogues, including topotecan (9-Dimethylaminomethyl-10-hydroxycamptothecin, HCl salt 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)- dione, 4-ethyl-4,9-dihydroxy-10-[(dimethylamino)methyl]-,HCl salt (S) molecular formula: $C_{23}H_{23}N_3O_5 \cdot HCl$, molecular weight: 457.9), are anti-neoplastic agents, believed to exert cytotoxic effects through the inhibition of topoisomerase I. This is the only known class of drug that exhibits this mechanism of action. However, inhibition of topoisomerase activity is not an unknown mechanism of action since many classes of drugs *(eg. epipodophyllotoxins)* operate through inhibition of topoisomerase II *(topo II)*.

[101] Topoisomerases are enzymes which break strands of DNA so that the strands can be rotated around each other and then the break resealed. They can be divided into two classes according to the nature of the mechanisms of action they employ.

[102] Type I topoisomerase is a monomeric protein of about 100 Kilodaltons *(KDa)*. It is capable of making a transient break in a single strand of the DNA helix. This reduces the torsional strain on the DNA and allows the DNA to unwind ahead of the replication fork. This enzyme is capable of relaxing highly negatively supercoiled DNA. In the eukaryotic version of this enzyme, a phosphotyrosyl bond is formed between the enzyme and the 3' end of the DNA break. In this process there is a transfer of a phosphodiester bond in the DNA to the protein. The structure of the DNA is manipulated and the DNA is rejoined. Since the reaction requires only the transfer of bonds, not irreversible hydrolysis, no input of energy is required. Topo I is believed to function in DNA replication, RNA transcription, genetic recombination, chromosomal condensation/decondensation and in viral encapsulation. Its presence is not cell-cycle dependent and it is found in quiescent as well as proliferating cells. It appears, however, that this enzyme is not required for the viability of cells. Topo II seems

shown activity against a variety of cancers, including colorectal cancer. The success of topotecan in patients with previously treated small-cell lung cancer (response rate of as high as 39 percent) and ovarian cancer (response rate as high as 61 percent) has increased interest in Phase III trials with this drug.

[108] Hydroxyurea (Hydrea) - Hydroxyurea (molecular formula: $CH_4N_2O_2$, molecular weight: 76.06, CAS No. 127-07-1) is an Antineoplastic Agent. It is readily available drug that has been in use for three decades in treating certain kinds of leukemia and other cancers; it may also be promising for treatment of sickle cell disease. The exact mechanism of action has been unknown. It has been known that hydroxyurea immediately inhibits DNA synthesis without inhibiting the synthesis of RNA or protein, but until recently it was not known how it did this.

[109] Gemcitabine (Gemzar) (Gemcitabine hydrochloride; 2'-deoxy-2',2'-difluorocytidine) is an Antineoplastic Agent. Gemcitabine induces programmed cell death and activates protein kinase C in BG-1 human ovarian cancer cells. It is a known antitumor nucleoside where the mechanism of action of gemcitabine is via inhibition of DNA and RNA synthesis.

[110] Gemcitabine is a novel deoxycytidine analogue, a pyrimidine antimetabolite related to cytarabine, which was originally investigated for its antiviral effects but has since been developed as an anticancer therapy. Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is a pro-drug and is metabolized intracellularly to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effects of gemcitabine are exerted through dFdCDP-assisted incorporation of dFdCTP into DNA, resulting in inhibition of DNA synthesis and induction of apoptosis.

[111] Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumor cells.It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G 1/S-phase boundary.In vitro the cytotoxic action of gemcitabine is both concentration and time dependant.

[112] In animal tumor models, the antitumor activity of gemcitabine is schedule dependant. When administered daily gemcitabine causes death in animals with minimal anti-tumor activity. However when every 3rd or 4th day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent anti-tumor activity against a broad range of mouse tumors.

28, or when the therapeutic capable agent 28 is disposed within the interior (or the exterior of the expandable structure 16 as the case may be), 37 of the expandable structure 16.

[116] Now referring to FIG. 2C, the source may further comprises a rate-controlling element 43, may be formed over at least a portion of the expandable structure 16 for controlling the release of the therapeutic capable agent 28 from the matrix 40 or the interior 37 of the expandable structure. By way of example, the source may be the rate-controlling element itself when the therapeutic capable agent is a polymeric therapeutic capable agent.

[117] The rate-controlling element may be formed of a non-degradable, partially degradable, substantially degradable material, or a combination thereof. The material may be synthetic or natural; non-polymeric, polymeric or metallic; or a combination thereof. By way of examples, a metallic material that at least partially degrades with time may be used as the rate-controlling element; as well as non-polymers having large molecular weight, polar or non-polar functional groups, electrical charge, steric hindrance groups, hydrophobic, hydrophilic, or amphiphilic moieties.

[118] Suitable biodegradable rate-controlling element materials include, but are not limited to, poly(lactic acid), poly(glycolic acid) and copolymers, poly dioxanone, poly (ethyl glutamate), poly (hydroxybutyrate), polyhydroxyvalerate and copolymers, polycaprolactone, polyanhydride, poly(ortho esters); poly (iminocarbonates), polycyanoacrylates, polyphosphazenes, copolymers and other aliphatic polyesters, or suitable copolymers thereof including copolymers of poly-L-lactic acid and poly-e-caprolactone; mixtures, copolymers, and combinations thereof.

[119] Suitable nondegradable or slow degrading rate-controlling element materials include, but are not limited to, polyurethane, polyethylenes imine, cellulose acetate butyrate, ethylene vinyl alcohol copolymer, silicone, polytetrafluorethylene (PTFE), parylene, parylast, poly (methyl methacrylate butyrate), poly-N-butyl methacrylate, poly (methyl methacrylate), poly 2-hydroxy ethyl methacrylate, poly ethylene glycol methacrylates, poly vinyl chloride, poly(dimethyl siloxane), poly(tetrafluoroethylene), poly (ethylene oxide), poly ethylene vinyl acetate, poly carbonate, poly acrylamide gels, N-vinyl-2-pyrrolidone, maleic anhydride, Nylon, cellulose acetate butyrate (CAB) and the like, including other synthetic or natural polymeric substances; mixtures, copolymers, and combinations thereof. In an embodiment the rate-controlling element is formed from a material selected from the group consisting of silicone, polytetrafluoroethylene, parylast, polyurethane, parylene, cellulose acetate butyrate; mixtures, copolymers and combinations thereof.

by surface degradation or hydrolysis, in which a surface of the rate-controlling element degrades or hydrolyzes over time while maintaining bulk integrity. In another embodiment, hydrophobic rate-controlling elements are preferred as they tend to release therapeutic capable agent at desired release rate. A non-degradable rate-controlling element may release therapeutic capable agent by diffusion. By way of example, if the rate-controlling element is formed of non-polymeric material, the therapeutic capable agent may be released as a result of the interaction (e.g., chemical reaction, steric hinderence, hyrophobicity, hydrophilicity, amphilicity) of the therapeutic capable agent with the rate-controlling element material (e.g, a non-polymer compound). In an embodiment, when the rate-controlling element does not form, at least a sufficient matrix with the therapeutic capable agent, the therapeutic capable agent may be released by diffusion through the rate-controlling element.

[124] By way of example, a rate-controlling element having low molecular weight and/or relatively high hydrophilicity in the tissue or blood, may diffuse through the source (e.g., a matrix), thus, increasing the surface area or volume for the therapeutic capable agent to be released from, thus, affecting the release rate of the therapeutic capable agent.

[125] In yet another embodiment the therapeutic capable agent is made available to the susceptible tissue site as the native environment of the area where the device is implanted changes. For example, a change in the pH of the area where the device is implanted may change over time so as to bring about the release of the therapeutic capable agent directly (as for example when a polymeric drug acts as the matrix including both the therapeutic capable agent and the rate-controlling element), or indirectly by affecting the erosion or diffusion characteristic of the rate-controlling element as either or both the matrix or non-matrix. For example, as the pH increases or decreases, the erosion of the rate-controlling element changes allowing for initial and subsequent phase releases.

[126] FIG. 2D illustrates features of an embodiment having the therapeutic capable agent 28 disposed between one of the tissue or luminal facing surfaces of the expandable structure and the rate-controlling element 43.

[127] As shown in FIG. 2E, the source 25 includes the rate-controlling element 43 formed adjacent at least a portion of one of the tissue or luminal facing surfaces of the expandable structure 16 and forming the matrix 40 with the therapeutic capable agent 28. As noted earlier, the therapeutic capable agent 28 may itself act as a rate-controlling element, as for example, when the polymeric therapeutic capable agent forms a matrix.

[128] The matrix may be formed between the rate-controlling element 43 and the expandable structure 16 and forming a matrix interface 46 therebetween and/or between the

cyclooxygenase inhibitors such as acetylsalicylic acid, ADP inhibitors such as clopidogrel (e.g., Plavix™) and ticlopdipine (e.g., ticlid™), phosphodiesterase III inhibitors such as cilostazol (e.g., Pletal™), glycoprotein IIb/IIIa agents such as abciximab (e.g., Rheopro™); eptifibatide (e.g., Integrilin™), and adenosine reuptake inhibitors such as dipyridmoles; healing and/or promoting agents including anti-oxidants, nitrogen oxide donors; antiemetics; antinauseants; derivatives and combinations thereof.

[134] The another therapeutic agent may be released prior to, concurrent with, or subsequent to, the therapeutic capable agent, at similar or different rates and phases.

[135] In another embodiment, features of which are shown in FIGS. 2L and 2M, the therapeutic capable agent 28 is disposed within or on the expandable structure 16 within a reservoir 58. The rate-controlling element 43 may be disposed adjacent the reservoir 58 and/or the therapeutic capable agent 28 for affecting the release of the therapeutic capable agent. As stated earlier, the exemplary figures and descriptions are not meant to limit the term "adjacent."

[136] In a further embodiment, features of which are shown in FIG. 2N, the another compound comprises the enabling compound 61 respondable to an external form of energy, or native condition, to affect the release of the therapeutic capable agent. The respondable compound may be associated with the therapeutic capable agent, the rate-controlling element, the expandable structure, or a combination thereof. As shown in FIG. 2N, the respondable compound is associated with the therapeutic capable agent. The enabling compound 61 may be formed from magnetic particles coupled to the therapeutic capable agent 28. The energy source may be a magnetic source for directing a magnetic field at the prosthesis 13 after implantation to effect release of the therapeutic capable agent 28. The magnetic particles 61 may be formed from magnetic beads and will typically have a size in a range from about 1 nm to about 100 nm. The magnetic source exposes the prosthesis 13 to its magnetic field at an intensity typically in the range from about 0.01T to about 2T, which will activate the magnetic particles 61 and thereby effect release of the therapeutic capable from the prosthesis. The another enabling compound may be present in other configurations of prosthesis 13 as described above.

[137] Other suitable external energy sources, which may or may not require a second compound or their performance may not be affected by the presence or absence of a second compound, include ultrasound, magnetic resonance imaging, magnetic field, radio frequency,

on each ring segment 73 will be joined by the sigmoidal links76 to the adjacent ring segment. Stent 70 as shown in FIG. 3 shows the stent 70 is in a collapsed or non-expanded configuration.

[142] The term "radially expandable" as used herein includes segments that can be converted from a small diameter configuration to a radially expanded, usually cylindrical, configuration which is achieved when the expandable structure 16 is implanted at a desired target site. The expandable structure 16 may be minimally resilient, e.g., malleable, thus requiring the application of an internal force to expand and set it at the target site. Typically, the expansive force can be provided by a balloon, such as the balloon of an angioplasty catheter for vascular procedures. The expandable structure 16 preferably provides sigmoidal links between successive unit segments which are particularly useful to enhance flexibility and crimpability of the stent.

[143] Alternatively, the expandable structure 16 can be self-expanding. Structures for use in the devices of the present invention, including the expandable structure 16 (such as self-expanding structures) are provided by utilizing a resilient material, such as a tempered stainless steel, or a superelastic alloy such as a Nitinol™ alloy, and forming the body segment so that it possesses its desired, radially-expanded diameter when it is unconstrained, i.e. released from the radially constraining forces of a sheath. In order to remain anchored in the body lumen, the expandable structure 16 will remain partially constrained by the lumen. The self-expanding expandable structure 16 can be tracked and delivered in its radially constrained configuration, e.g., by placing the expandable structure 16 within a delivery sheath or tube and removing the sheath at the target site.

[144] The dimensions of the expandable structure will depend on its intended use. Typically, the expandable structure will have a length in a range from about 5 mm to about 100 mm, usually being from about 8 mm to about 50 mm, for vascular applications. The diameter of a cylindrically shaped expandable structure for vascular applications, in a non-expanded configuration, usually ranges from about 0.5 mm to about 10 mm, more usually from about 0.8 mm to about 8 mm; with the diameter in an expanded configuration ranging from about 1.0 mm to about 100 mm, preferably from about 2.0 mm to about 30 mm. The expandable structure usually will have a thickness in a range from about 0.025 mm to 2.0 mm, preferably from about 0.05 mm to about 0.5 mm.

[145] The ring segments, and other components of structures such as the expandable structure 16, may be formed from conventional materials used for body lumen stents and grafts, typically being formed from malleable metals or alloyes, such as 300 series stainless

reduced to no hindrance to endothelialization of the vessel wall due to the minimization of washout of the therapeutic capable agent and the increased efficiency of its release.

[147] The devices of the present invention may be configured to release or make available the therapeutic capable agent at one or more phases, the one or more phases having similar or different performance (e.g., release) profiles. The therapeutic capable agent may be made available to the tissue at amounts which may be sustainable, intermittent, or continuous; in one or more phases and/or rates of delivery; effective to reduce any one or more of smooth muscle cell proliferation, inflammation, immune response, hypertension, or those complementing the activation of the same. Any one of the at least one therapeutic capable agents may perform one or more functions, including preventing or reducing proliferative/restenotic activity, reducing or inhibiting thrombus formation, reducing or inhibiting platelet activation, reducing or preventing vasospasm, or the like.

[148] The total amount of therapeutic capable agent made available to the tissue depends in part on the level and amount of desired therapeutic result. The therapeutic capable agent may be made available at one or more phases, each phase having similar or different release rate and duration as the other phases. The release rate may be pre-defined. In an embodiment, the rate of release may provide a sustainable level of therapeutic capable agent to the susceptible tissue site. In another embodiment, the rate of release is substantially constant. The rate may decrease and/or increase over time, and it may optionally include a substantially non-release period. The release rate may comprise a plurality of rates. In an embodiment the plurality of release rates include at least two rates selected from the group consisting of substantially constant, decreasing, increasing, substantially non-releasing.

[149] The total amount of therapeutic capable agent made available or released will typically be in an amount ranging from about 0.1 ug to about 10 g, generally from about 0.1 ug to about 10 mg, preferably from about 1 ug to about 10 mg, more preferably from about 1 ug to about 2 mg, from 10 ug to about 2 mg, or from about 50 ug to about 1 mg.

[150] In an embodiment, the therapeutic capable agent may be released in a time period, as measured from the time of implanting of the device, ranging from about 1 day to about 200 days; from about 1 day to about 45 days; or from about 7 days to about 21 days.

[151] In an embodiment the release rate of the therapeutic capable agent per day may range from about 0.001 micrograms (ug) to about 200 ug, preferably, from about 0.5 ug to about 200 ug, and most preferably, from about 1 ug to about 60 ug.

[152] The therapeutic capable agent may be made available at an initial phase and one or more subsequent phases. When the therapeutic capable agent is delivered at different phases,

[156] When the device includes the source including a plurality of compounds (e.g., first therapeutic capable agent and an another compound such as another therapeutic capable agent or enabling compound), the plurality of compounds may be released at different times and/or rates, from the same or different layers when present. Each of the plurality of compounds may be made available independently of another, simultaneous with, or subsequent to the interventional procedure, and may be simultaneous or sequential with one another. For example, a first therapeutic capable agent (e.g., TriptolideTM may be released within a time period of 1 day to 45 days with the second therapeutic capable agent (e.g, mycophenolic acid) released within a time period of 2 days to 3 months, from the time of interventional procedure.

[157] The devices of the present invention may be provided together with instructions for use (IFU), separately or as part of a kit. The kit may include a pouch or any other suitable package, such as a tray, box, tube, or the like, may be used to contain the device and the IFU, where the IFU may be printed on a separate sheet or other media of communication and/or on the packaging itself. In an embodiment of a kit, the kit may also include a mounting hook such as a crimping device and/or an expansible inflation member which may be permanently or releaseably coupled to the device of the present invention. In an embodiment, the kit may comprise the device and an IFU regarding the use of a second compound prior to, concurrent with, or subsequent to, the interventional procedure, and optionally the second compound. In an embodiment, the kit comprises the device and the second compound with or without the IFU for the second compound and/or the device.

[158] In one embodiment, the second compound, may be a therapeutic capable agent, an another compound (e.g., the another therapeutic capable agent and/or the another enabling and/or enhancing compound), or a bio-active compound such as an anti-nausea drug; and being similar or different than that made available to the susceptible tissue site by the device; may be administered prior to, concurrent with, or subsequent to the implanting of the device (e.g., prosthesis) of the present invention.

[159] The second compound may be administered from a pathway similar to or different than that used for the delivery of the therapeutic capable agent as part of the device. By way of example, the second compound may be in the form of a tablet to be taken orally, a transdermal patch to be placed on the patient's skin, subcutaneously, systemically by direct introduction to the blood stream, by way of inhalation, or through any other pathways and bodily orifices. Alternatively, the second compound may be made available to the intracorporeal body by a catheter. In an embodiment, the balloon of a balloon catheter (e.g.,

therapeutic capable agent onto the prosthesis. Usually, the therapeutic capable agent is dissolved in a solvent. Suitable solvents include aqueous solvents (e.g., water with pH buffers, pH adjusters, organic salts, and inorganic salts), alcohols (e.g., methanol, ethanol, propanol, isopropanol, hexanol, and glycols), nitriles (e.g., acetonitrile, benzonitrile, and butyronitrile), amides (e.g., formamide and N-dimethylformamide), ketones, esters, ethers, DMSO, gases (e.g., CO_2), and the like. For example, the prosthesis may be sprayed with or dipped in the solution and dried so that therapeutic capable crystals are left on a surface of the prosthesis. Alternatively, matrix solution including a rate-controlling element material and the therapeutic capable agent may be prepared by dissolving the rate-controlling element material and the therapeutic capable agent. The expandable structure 16 may then be coated with the matrix solution by spraying, dipping, deposition, or painting the matrix onto the prosthesis. By way of example, when the matrix is formed from polymeric material, the matrix solution is finely sprayed on the prosthesis while the prosthesis is rotating on a mandrel. The thickness of the matrix coating may be controlled by the time period of spraying and a speed of rotation of the mandrel. The thickness of the matrix-agent coating is typically in a range from about 0.01 um to about 100 um, preferably in a range from about 0.1 um to about 50 um. Once the prosthesis has been coated with the matrix coating, the stent may be placed in a vacuum or oven to complete evaporation of the solvent.

[163] By way of example, a stainless steel Duraflex™ stent (available from Avantec Vascular Corporation, having a place of operation in California), having dimensions of 3.0 mm x 14 mm is sprayed with a solution of 25 mg/ml therapeutic capable agent in a 100% ethanol or methanol solvent. The stent is dried and the ethanol is evaporated leaving the therapeutic capable agent on the stent surface. A 75:25 PLLA/PCL copolymer (sold commercially by POLYSCIENCES) is prepared in 1,4 Dioxane (sold commercially by ALDRICH CHEMICALS). The therapeutic capable agent loaded stent is loaded on a mandrel rotating at 200 rpm and a spray gun (sold commercially by BINKS MANUFACTURING) dispenses the copolymer solution in a fine spray on to the therapeutic capable agent loaded stent as it rotates for a 10-30 second period. The stent is then placed in an oven at 25-35°C up to 24 hours to complete evaporation of the solvent.

[164] In operation, methods of delivering therapeutic capable agents to a susceptible tissue site, comprise providing a luminal prosthesis incorporating features of the present invention as described above. The prosthesis is delivered to a corporeal site, such as a body lumen, including the susceptible tissue site. The prosthesis is implanted within the body lumen. The therapeutic capable agent is made available to the susceptible tissue site over a period of time.

agent. Typically the delay is sufficiently long to allow the sufficient generation of intimal tissue or cellularization, at the treated site to reduce occurrence of thrombotic event.

[170] In one embodiment, delay is sufficiently long to allow the generated neointima to cover at least partially the implanted expandable structure. In an embodiment, the therapeutic capable agent may be released in a time period, as measured from the time of implanting of the device, ranging from about 1 day to about 200 days; from about 1 day to about 45 days; or from about 7 days to about 21 days. In an embodiment, the method further includes directing energy at the device to effect release of the therapeutic capable agent from the device. The energy may include one or more of ultrasound, magnetic resonance imaging, magnetic field, radio frequency, temperature change, electromagnetic, x-ray, heat, vibration, gamma radiation, or microwave. In an embodiment, the therapeutic capable agent may be released at a total amount ranging from about 0.1 ug to about 10 g, from about 0.1 ug to about 10 mg, from about 1 ug to about 10 mg, from about 1 ug to about 2 mg, from about 10 ug to about 2 mg, or from about 50 ug to about 1 mg.

[171] In another embodiment of a method of treatment, the releasing includes release of at least one another compound, as described. The anther compound may be another therapeutic capable agent or an enabling compound, as described. The another compound may be released prior to, concurrent with, subsequent to the therapeutic capable agent, or sequentially with the therapeutic capable agent.

[172] In an embodiment, a second compound, as described, may be administered to the patient, prior to, concurrent with, or subsequent to the interventional procedure. The second compound may be administered from pathways, at time periods, and at levels, as described.

[173] It should be appreciated that depending on the nature of the site under treatment, the device of the present invention may be introduced to the site during the introduction of the first balloon catheter without the need for pre-dilatation.

[174] In general, it will be possible to combine elements of the differing prostheses and treatment methods as described above. For example, a prosthesis having reservoir means for releasing therapeutic capable agents may further incorporate a rate-controlling barrier. Additionally, methods of the present invention may combine balloon angioplasty and/or other interventional treatments to resolve a stenotic site with the presently described luminal therapeutic capable delivery treatments.

(another barrier or matrix). Use of top coats provides further control of release rate, improved biocompatibility, and/or resistance to scratching and cracking upon stent delivery or expansion.

[179] EXAMPLE 5 – The therapeutic capable agent may be combined with a second therapeutic capable agent (cytotoxic drugs, cytostatic drugs, or psoriasis drugs). One agent is in or coupled to a first coat while other agent is in or coupled to a second coat. The therapeutic capable agent is released for the first 1-3 weeks after being implanted within a vessel while the second therapeutic capable agent is released or continues to be released for a longer period.

[180] EXAMPLE 6 - A combination of multiple therapeutic capable agents that are individually included in different coats can be used as the matrix. The coats may release the multiple agents simultaneously and/or sequentially. The agents may be selected from a therapeutic capable agent class of inhibitors of de novo nucleotide synthesis or from classes of glucocorticosteroids, immunophilin-binding drugs, deoxyspergualin, FTY720, protein drugs, or peptides. This can also apply to any combination of agents from the above classes that are coupled to a stent with the addition of other cytotoxic drugs.

[181] EXAMPLE 7 - A matrix including the therapeutic capable agent, mycophenolic acid, and matrix polymer, CAB (cellulose acetate butyrate); at a mycophenolic acid loading of 70 % to 80% by weight was prepared by dissolving the therapeutic capable agent in acetone at 15 mg/ml concentration, dissolving CAB in acetone at 15 mg/ml concentration, and thereafter mixing together the mycophenolic acid and CAB solutions in 3:1 portion matrix solution. The amount of therapeutic capable agent varied from about 0.1 microgram to about 2 mg, preferably, at 600 microgram. The matrix solution was then coated onto two sets of stents (Sets A and B) by spraying them with an atomizer sprayer (EFD manufacturer) while each stent was rotated. Each stent was allowed to let dry. One matrix-coated stent was then coated with parylene as the rate-controlling barrier (about 1.1 um) using methods similar to those described in Example 2. Orifices were created on the top surface (parylene rate-controlling barrier) of the stent of Set B by subjecting the surface to laser beams or needle. The orifice size can range from about 0.1 um to about 100 um in diameter. The orifice in Set B stent was about 10 um in diameter. An orifice can be about 0.003 to about 2 inches apart from the next orifice (measured as the curvilinear distance as you trace along the stent strut pattern).

[182] The mycophenolic acid loaded stents were placed in an elution solution of porcine serum and allowed to age for a period of 1 to 7 days. Samples from the serum were taken at

[185] EXAMPLE 10 - In another group of therapeutic capable agents, the amount of incorporated thymidine for samples of varying concentrations (0.003, 0.031, 0.31, 1.6, 3.1, 31, and 156 micromolar) was measured. As can be seen from the data represented in FIGS. 10A-10B, and corresponding to Mycophenolic acid and Methylprednisolone, respectively, the IC50 for these therapeutic capable agent was 1.0 micromolar.

[186] EXMAPLE 11 - In order to assess the effect of various therapeutic capable agents, cell cultures were subjected to some therapeutic capable agents, using methods similar to those described in Examples 9 and 10. As can be seen from data represented in FIGS. 11A-11B, and corresponding, respectively, to Triptolide (T), Dexamethasone (D), Methotrexate (M); and Mycophenolic Acid (MA); the therapeutic capable agents did not lead to significant cell death. In addition, it can be seen that at the IC50 concentrations, most of the cells were alive yet 50% proliferating.

[187] EXAMPLE 12 - A therapeutic capable agent, mycophenolic acid, was prepared by dissolving the therapeutic capable agent in acetone at 15 mg/ml concentration. The amount of therapeutic capable agent varied from about 0.1 ug to about 2 mg, preferably, at 600 ug. The drug solution was then coated onto or over a stent as described in Example 8 by spraying them with an atomizer sprayer (EFD manufacturer) while the stent was rotated. The stent was allowed to let dry. The stent was then placed over the tri-fold balloon on a PTCA catheter and crimped thereon. After crimping, the drug remained intact and attached to the stent. Expansion of the stent against a simulated Tecoflex vessel showed no cracking of the drug. Exposure of fluid flow over the stent before stent deployment against the simulated vessel did not result in drug detachment from the stent.

[188] Although certain preferred embodiments and methods have been disclosed herein, it will be apparent from the foregoing disclosure to those skilled in the art that variations and modifications of such embodiments and methods may be made without departing from the true spirit and scope of the invention. Therefore, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

providing a luminal prosthesis incorporating or coupled to the substance, wherein the prosthesis contains a matrix which undergoes degradation in a vascular environment; and

implanting the prosthesis in a body lumen so that at least a portion of the matrix degrades over a predetermined time period and substantial substance release begins after the matrix substantially begins to degrade.

11. A method as in Claim 10, wherein the substance is incorporated in a reservoir in or on a scaffold and the reservoir is covered by the matrix so that substantial substance release begins after the matrix has degraded sufficiently to uncover the reservoir.

12. A method as in Claim 10, wherein the substance is contained in the matrix and the matrix coats a scaffold, wherein an outer layer of the matrix is substantially free from the substance so that substance release will not substantially begin until the outer layer has degraded.

13. A method as in Claim 10, wherein the substance is contained within or on a scaffold coated by the matrix.

14. A method as in Claim 10, wherein the prosthesis is coated with the matrix by spraying, dipping, deposition, or painting.

15. A method as in Claim 10, wherein the prosthesis incorporates the substance by coating, spraying, dipping, deposition, or painting the substance on the prosthesis.

16. A method for treatment of a patient, comprising:

providing a vascular prosthesis comprising a structure and at least one source of at least one therapeutic capable agent associated with the structure;

implanting the vascular prosthesis within the patient's vasculature including a susceptible tissue site;

releasing at least one therapeutic capable agent.

17. The method of Claim 16 wherein releasing comprises releasing at least one therapeutic capable agent is selected from the group consisting of immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents,

phosphodiesterase III inhibitors, glycoprotein IIb/IIIa agents; eptifibatides, and adenosine reuptake inhibitors; healing and/or promoting agents including anti-oxidants, nitrogen oxide donors; antiemetics; antinauseants; derivatives and combinations thereof.

26. The method of Claim 23 wherein the releasing comprises releasing another compound selected from the group consisting of heparin and its derivatives; Thalidomide™; riboflavin; tiazofurin; zafurin; acetylsalicylic acid, clopidogrel such as Plavix™, ticlopdipine such as ticlid™, cilostazol such as Pletal™, abciximab such as Rheopro™; eptifibatide such as Integrilin™, dipyridmoles; NSAID, TaxolTM, Actinomycine DTM; derivatives and combinations thereof.

27. The method of Claim 23 wherein the another compound is an enabling compound.

28. The method of Claim 23 wherein the another compound is released prior to the therapeutic capable agent.

29. The method of Claim 23, 24, 25, 26, or 27 wherein the another compound is released concurrent with the therapeutic capable agent.

30. The method of Claim 23, 24, 25, 26, or 27 wherein the another compound is released sequentially with the therapeutic capable agent.

31. The method of Claim 16 wherein the device is configured to release the therapeutic capable agent at a total amount ranging from about 0.1 ug to about 10 g.

32. The method of Claim 16 wherein the therapeutic capable agent is released at a total amount ranging from about 0.1 ug to about 10 mg.

33. The method of Claim 16 wherein the therapeutic capable agent is released at a total amount ranging from about 1 ug to about 2 mg.

34. The method of Claim 16 wherein the therapeutic capable agent is released at a total amount ranging from about 1 ug to about 10 mg.

35. The method of Claim 16 wherein the therapeutic capable agent is released at a total amount ranging from about 10 ug to about 2 mg.

46. The method of Claim 40 wherein the administering the second compound comprises administering to the patient in a time period from about 3 months prior to about up to the interventional procedure.

47. The method of Claim 40 wherein the administering the second compound comprises administering to the patient in a time period from about 7 days to about 24 hours prior to the interventional procedure.

48. The method of Claim 40 wherein the administering the second compound comprises administering an acute dose ranging from about 0.5 mg to about 5 g.

49. The method of Claim 40 wherein the administering the second compound comprises administering an acute dose ranging from about 1 mg to about 3 g.

50. The method of Claim 40 wherein the administering the second compound comprises administering an acute dose ranging from about 1 g to about 1.5 g.

51. The method of Claim 40 wherein the administering the second compound comprises administering an acute dose ranging from about 2 g to about 3 g.

52. The method of Claim 40 wherein the administering the second compound comprises administering a dose per day ranging from about 1 g to about 1.5 g.

53. The method of Claim 40 wherein the administering the second compound comprises administering a dose per day ranging from about 1 mg to about 3 mg.

54. The method of Claim 40 wherein the administering the second compound comprises administering a dose per day ranging from about 2 g to about 3 g.

55. The method of Claim 40 wherein the administering the second compound comprises administering a dose per day ranging from about 2 mg to about 6 mg.

56. A method for delivering a therapeutic capable agent to a susceptible tissue site within a corporeal body, comprising:

positioning a source of the therapeutic capable agent within a vascular lumen;

releasing the therapeutic capable agent to the susceptible tissue site.

67. The method of Claim 66 wherein the device is positioned within the corporeal body during a vascular intervention.

68. The method of Claim 67 wherein the release of the therapeutic capable agent is delayed for a predetermined period of time following the positioning of the device within the corporeal body.

69. The method of Claim 68 wherein the delay is sufficiently long to allow sufficient generation of intimal tissue to reduce occurrence of thrombotic event.

70. The method of Claim 63 or 64 wherein the corporeal body is a body lumen.

71. The method of Claim 63 or 64 wherein the corporeal body is an organ.

72. The method of Claim 63 or 64 further including directing energy at the device to effect release of the therapeutic capable agent from the device.

73. The method of Claim 72 wherein the energy is at least one of ultrasound, magnetic resonance imaging, magnetic field, radio frequency, temperature change, electromagnetic, x-ray, heat, vibration, gamma radiation, microwave, or a combination thereof.

74. A device for intracorporeal use, comprising:
a structure; and
at lease one source of at least one therapeutic capable agent associated with the structure.

75. The device of Claim 74 wherein the source is configured to provide the at least one therapeutic capable agent to a targeted intracorporeal site within an intracorporeal body.

76. The device of Claim 75 wherein the targeted intracorporeal site comprises a body lumen.

77. The device of Claim 75 wherein the targeted intracorporeal site comprises a body organ.

90. The device of Claim 75 or 87 wherein the expandable structure is formed from an at least partially degradable material.

91. The device of Claim 90 wherein the at least partially degradable material is at least partially biodegradable.

92. The device of Claim 90 wherein the at least partially biodegradable material comprises a metal or alloy degradable in the corporeal body.

93. The device of Claim 92 wherein the metal or alloy alloy comprises stainless steel.

94. The device of Claim 93 wherein the therapeutic capable agent is made available to the susceptible tissue site as the stainless steel degrades within the corporal body over time.

95. The device of Claim 85 wherein the therapeutic capable agent comprises a polymeric material formed at least in part from therapeutic capable agent.

96. The device of Claim 95 wherein the therapeutic capable agent units are disassociated in the corporeal body.

97. The device of Claim 95 wherein the therapeutic capable agent units are disassociated in a vascular environment.

98. The device of Claim 95 wherein the therapeutic capable agent units are disassociated over time.

99. The device of Claim 85 wherein the source is a polymeric material including the therapeutic capable units associated with a polymeric backbone.

100. The device of Claim 85 wherein the source is a polymeric material including the therapeutic capable units associated with a metallic backbone.

101. The device of Claim 74 wherein the device is configured to release the therapeutic capable at release rate.

116. The device of Claim 114 wherein the rate-controlling element forms the outer most layer of the device.

117. The device of Claim 112 wherein the rate-controlling element is disposed adjacent at least a portion of the expandable structure.

118. The device of Claim 112, 113, 114, 116, or 117 wherein the rate-controlling element is formed from a material selected from the group consisting of polymerics, metallics, bioactive compounds, and non-bioactive compounds.

119. The device of Claim 118 wherein the rate-controlling element material comprises a polymeric material.

120. The device of Claim 119 further comprising a second rate-controlling element disposed adjacent at least a portion of the first rate-controlling element.

121. The device of Claim 118 wherein the rate-controlling element is formed from a biodegradable material.

122. The device of Claim 118 wherein the rate-controlling element is formed from a material selected from the group consisting of poly(lactic acid), poly(glycolic acid) and copolymers, poly dioxanone, poly (ethyl glutamate), poly (hydroxybutyrate), polyhydroxyvalerate and copolymers, polycaprolactone, polyanhydride, poly(ortho esters); poly (iminocarbonates), polycyanoacrylates, polyphosphazenes, copolymers and other aliphatic polyesters, or suitable copolymers thereof including copolymers of poly-L-lactic acid and poly-e-caprolactone; mixtures, copolymers, and combinations thereof.

123. The device of Claim 121 wherein the therapeutic capable agent is released by surface degradation or hydrolysis of the rate-controlling element.

124. The device of Claim 121 wherein the therapeutic capable agent is released by bulk degradation of the rate-controlling element.

125. The device of Claim 118 wherein the rate-controlling element is formed from a non-biodegradable or slow degrading material.

133. The device of Claim 132 wherein the metals or alloys are at least two and having different galvanic potential.

134. The device of Claim 118 wherein the rate-controlling element includes a plurality of layers.

135. The device of Claim 134 wherein at least one of the rate-controlling element plurality of layers includes the therapeutic capable agent.

136. The device of Claim 135 wherein the layers other than the at least one layer includes the same or a different therapeutic capable agent.

137. The device of Claim 86 wherein the source is a reservoir disposed adjacent the expandable structure.

138. The device of Claim 137 wherein the reservoir is at least partially on an exterior of the expandable structure.

139. The device of Claim 137 wherein the reservoir is at least partially in the interior of the expandable structure.

140. The device of Claim 137 wherein the reservoir is at least partially on either or both the luminal and the tissue facing surfaces of the expandable structure.

141. The device of Claim 137 wherein the reservoir is at least partially in the expandable structure.

142. The device of Claim 138 or 139 wherein a rate-controlling element is disposed at least partially adjacent the reservoir.

143. The device of Claim 140 or 141 wherein a rate-controlling element is disposed at least partially over the reservoir.

144. The device of 113 or 115 wherein the rate-controlling element has thickness ranging from about 10 nm to about 100 um.

145. The device of Claim 144 wherein the rate-controlling element has thickness ranging from about 50 nm to about 100 um.

156. The device of Claim 152 wherein the therapeutic capable agent has immunosuppressive, anti-proliferative, and anti-inflamatory effects.

157. The device of Claim 151 wherein the therapeutic capable agent is at least one agent selected from the group consisting of mycophenolic acid, mycophenolate mofetil, mizoribine, methylprednisolone, dexamethasone, Certican™, rapamycin, Triptolide™, Methotrexate™, Benidipine™, Ascomycin™, Wortmannin™, LY294002, Camptothecin™, Topotecan™, hydroxyurea, Tacrolimus™ (FK 506), cyclophosphamide, cyclosporine, daclizumab, azathioprine, prednisone, Gemcitabine™, derivatives and combinations thereof.

158. The device of Claim 151 or 157 wherein the at least one agent includes an active compound, the pro-drug of the active compound, a metabolite of the active compound, a derivative of the active compound, or a combination thereof.

159. The device of Claim 150 wherein source further includes another compound.

160. The device of Claim 159 wherein another compound is another therapeutic capable agent.

161. The device of Claim 159 wherein the another compound is an enabling compound.

162. The device of Claim 159 wherein the another compound is selected from the group consisting of anti-cancer agents; chemotherapeutic agents; thrombolytics; vasodilators; antimicrobials or antibiotics antimitotics; growth factor antagonists; free readical scavengers; biologic agents; radiotherapeutic agents; radiopaque agents; radiolabelled agents; anti-coagulants such as heparin and its derivatives; anti-angiogenesis drugs; angiogenesis drugs; PDGF-B and/or EGF inhibitors; anti-inflamatories including psoriasis drugs; anti-platelet agents including , cyclooxygenase inhibitors such as acetylsalicylic acid, ADP inhibitors ticlopdipine phosphodiesterase III inhibitors, glycoprotein IIb/IIIa agents; eptifibatides, and adenosine reuptake inhibitors; healing and/or promoting agents including anti-oxidants, nitrogen oxide donors; antiemetics; antinauseants; derivatives and combinations thereof.

172. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a rate between about 0.5 ug to about 200 ug/day.

173. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a rate between about 1 ug to about 100 ug/day.

174. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a rate between about 10 ug to about 60 ug/day.

175. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a rate between about 1 ug to about 60 ug/day.

176. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at different phases.

177. The device of Claim 176 wherein the device is configured to release the therapeutic capable agent at an initial phase having a lower rate of release than a subsequent phase.

178. The device of Claim 176 wherein the device is configured to release the therapeutic capable agent at an initial phase having a higher rate of release than a subsequent phase.

179. The device of Claim 177 wherein the device is configured to release the therapeutic capable agent at an initial phase having an initial rate of release ranging from about 0 to about 99% of a subsequent rate of release of a subsequent phase.

180. The device of Claim 177 wherein the device is configured to release the therapeutic capable agent at an initial phase having an initial rate of release ranging from about 0 to about 90% of a subsequent rate of release of a subsequent phase.

181. The device of Claim 177 wherein the device is configured to release the therapeutic capable agent at an initial phase having an initial rate of release ranging from about 0 to about 75% of a subsequent rate of release of a subsequent phase.

about 40 to about 300 ug/day, and a subsequent phase having a subsequent rate of release ranging from about 0.5 to 40 ug/day.

190. The device of Claim 178 wherein the device is configured to release the therapeutic capable agent at an initial phase having an initial rate of release ranging from about 40 to about 200 ug/day, and a subsequent phase having a subsequent rate of release ranging from about 10 to 40 ug/day.

191. The device of Claim 178 wherein the device is configured to release the therapeutic capable agent at an initial phase having an initial rate of release ranging from about 40 to about 200 ug/day, and a subsequent phase having a subsequent rate of release ranging from about 0.5 to 40 ug/day.

192. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a substantially constant rate ranging from about 0.01 ug to 200 ug/day.

193. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a total amount ranging from about 0.1 ug to about 10 g.

194. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a total amount ranging from about 0.1 ug to about 10 mg.

195. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a total amount ranging from about 1 ug to about 2 mg.

196. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a total amount ranging from about 10 ug to about 2 mg.

197. The device of Claim 170 wherein the device is configured to release the therapeutic capable agent at a total amount ranging from about 50 ug to about 1 mg.

198. The device of Claim 170 wherein the device is configured to deliver the therapeutic capable agent at a phase to a susceptible tissue site of a mammalian intracorporeal body to effectuate a mammalian tissue concentration ranging from about 0.001 ng of therapeutic capable agent / mg of tissue to about 100 ug of therapeutic capable agent / mg of tissue.

207. The device of Claim 206 wherein the device is configured to deliver the therapeutic capable agent at a second phase to the susceptible tissue site of the mammalian intracorporeal body to effectuate a mammalian tissue concentration of the therapeutic capable agent ranging from about 0.001 ng of therapeutic capable agent / mg of tissue to about 100 ug of therapeutic capable agent / mg of tissue.

208. The device of Claim 207 wherein the tissue concentration ranges from about 1 ng of therapeutic capable agent / mg of tissue to about 10 ug of therapeutic capable agent /mg of tissue.

209. The device of Claim 170 wherein device is configured to release the therapeutic capable agent at a substantially constant rate ranging from about 0.01 ug to 200 ug/day.

210. The device of Claim 176 wherein device is configured to deliver the therapeutic capable agent at an initial and a subsequent phase.

211. The device of Claim 176 wherein at the initial phase the release of the therapeutic capable agent is delayed.

212. The device of Claim 176, or 211 wherein the duration of the initial phase is configured to last less than about 24 weeks.

213. The device of Claim 176, or 211 wherein the duration of the initial phase is configured to last less than about 12 weeks.

214. The device of Claim 176, or 211 wherein the duration of the initial phase is configured to last from about 1 hour to about 24 weeks.

215. The device of Claim 176, or 211 wherein the duration of the initial phase is configured to last from about 1 hour to about 8 weeks.

216. The device of Claim 176, or 211 wherein the duration of the initial phase is configured to last from about 12 hours to about 2 weeks.

217. The device of Claim 176, or 211 wherein the duration of the initial phase is configured to last from about 1 day to about 1 week.

230. The device of Claim 228 wherein the device is configured to deliver the therapeutic capable agent at the initial phase to a susceptible tissue site of a mammalian intracorporal body to effectuate a mammalian tissue concentration of the therapeutic capable agent ranging from about 10 ng / mg to about 100 ug / mg.

231. The device of Claim 170 wherein the device is configured to have a termination phase delivering the therapeutic capable agent to a mammalian intracorporeal body at a rate less than a rate of clearance the intracorporeal body of the therapeutic capable agent.

232. The device of Claim 231 wherein the termination phase has a duration of about 14 days.

233. The device of Claim 231 wherein the rate of clearance is about 1 ng to about 100 ng per mg of tissue per day.

234. The device of Claim 231 wherein the rate of clearance is about 80 ng per mg of tissue per day.

235. The device of Claim 231 wherein the rate of clearance is about 10 ng per mg of tissue per day.

236. The device of Claim 150 wherein the source is associated with the expandable structure by coating, spraying, dipping, vapor deposition, plasma deposition, or painting of the source onto or in the expandable structure.

237. The device of Claim 236 wherein the source is mixed in a solvent selected from the group consisting of methanol, DMSO, CO_2.

238. A device for intracorporeal use, comprising:

an expandable structure;

a source of therapeutic capable agent disposed adjacent the expandable structure, and including a plurality of rate-controlling element layers at least one of which comprises parylast or parylene, each layer having a thickness in a range from about 50 nm to 10 microns.

249. The device of Claim 244 wherein the delay is sufficiently long to allow the formation of sufficient amount of endothelization on the device.

250. The device of Claim 244 wherein the delay is sufficiently long to allow the formation of sufficient amount of endotheliazation at the susceptible tissue site and on the device.

251. The device of Claim 244 wherein the delay is sufficiently long to allow the formation of sufficient amount of fibrin deposition at the susceptible tissue site.

252. The device of Claim 244 wherein the delay is sufficiently long to allow the formation of sufficient amount of fibrin deposition on the device.

253. The device of Claim 244 wherein the delay is sufficiently long to allow the formation of sufficient amount of fibrin deposition at the susceptible tissue site and on the device.

254. The device of Claim 244 wherein the source comprises a rate-controlling element disposed adjacent the expandable structure.

255. The device of Claim 244 wherein the rate-controlling element forms a matrix with the therapeutic capable agent.

256. The device of Claim 244 wherein the rate-controlling element forms a matrix with the therapeutic capable agent.

257. A kit for providing a therapeutic capable agent to a susceptible tissue site including:

a device according to any one of Claims 74, 150, 238, or 241; and

a second compound.

258. The kit of Claim 257 wherein second compound is selected from the group consisting of compounds according to any of Claims 151, 157, 162, 163, 164; and combinations thereof.

259. The kit of Claim 257 wherein the second compound is an antiemetics or an antinauseants.

270. The kit of Claim 264 wherein the second compound is administerable to the patient in a time period from about 3 months to about up to the interventional procedure.

271. The kit of Claim 264 wherein the bioactive compound is administerable to the patient in a time period from about 7 days to about 24 hours prior to an interventional procedure.

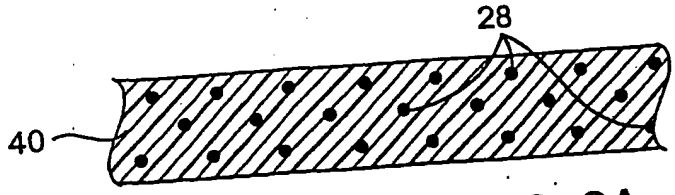

FIG. 2A

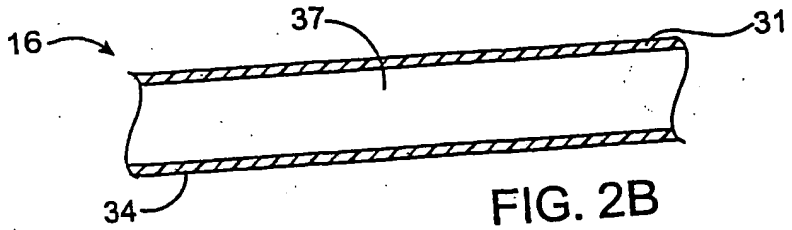

FIG. 2B

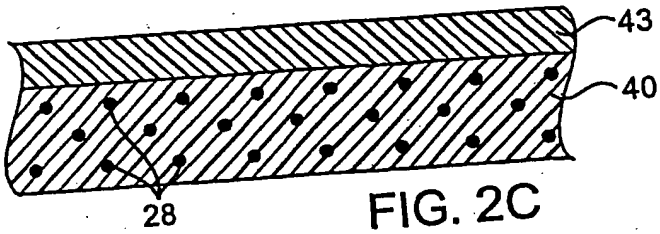

FIG. 2C

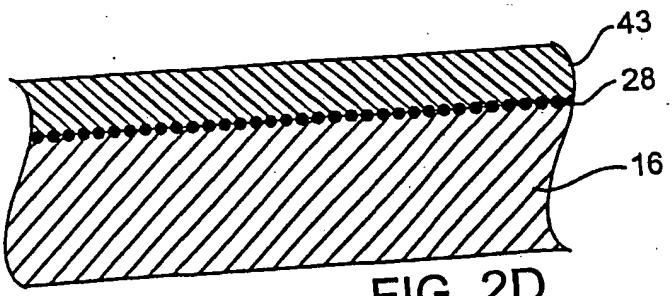

FIG. 2D

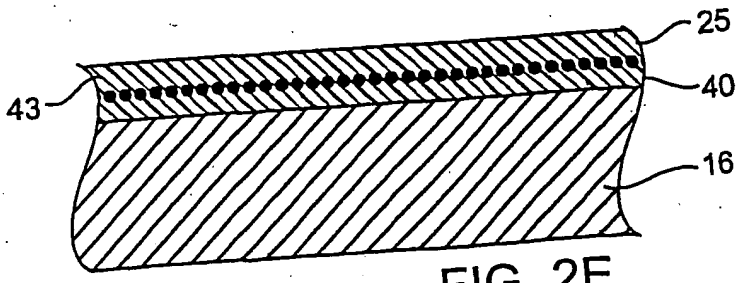

FIG. 2E

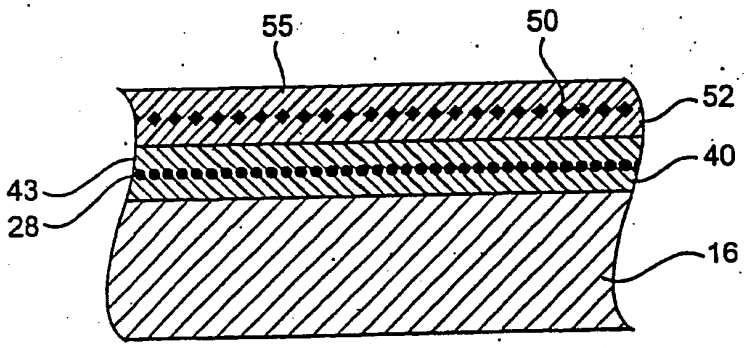

FIG. 2K

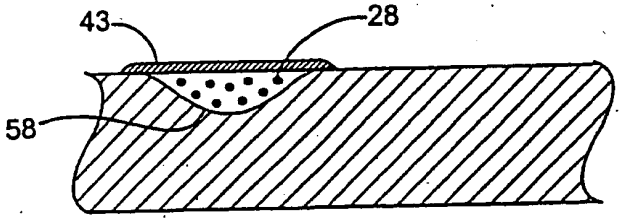

FIG. 2L

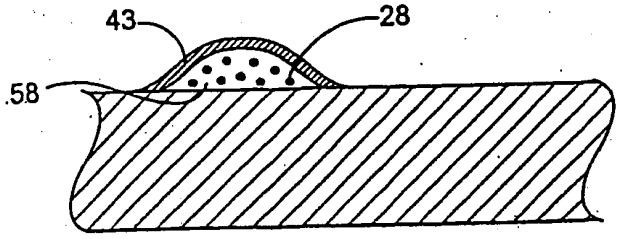

FIG. 2M

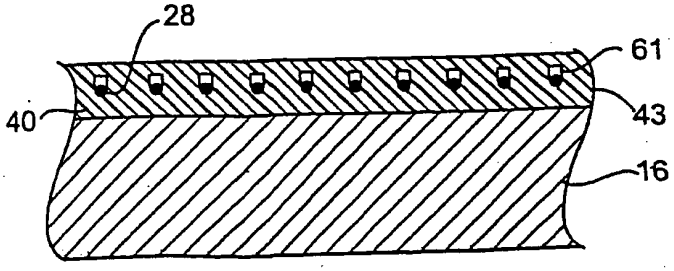

FIG. 2N

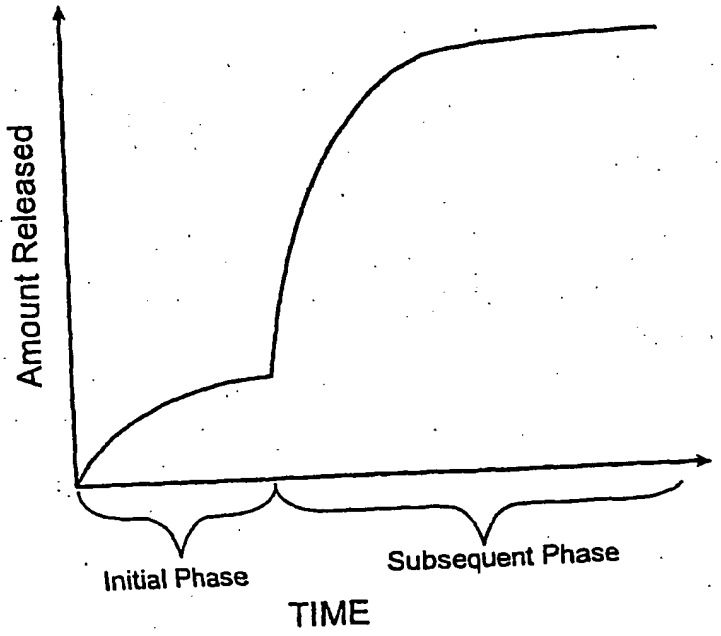

FIG. 4

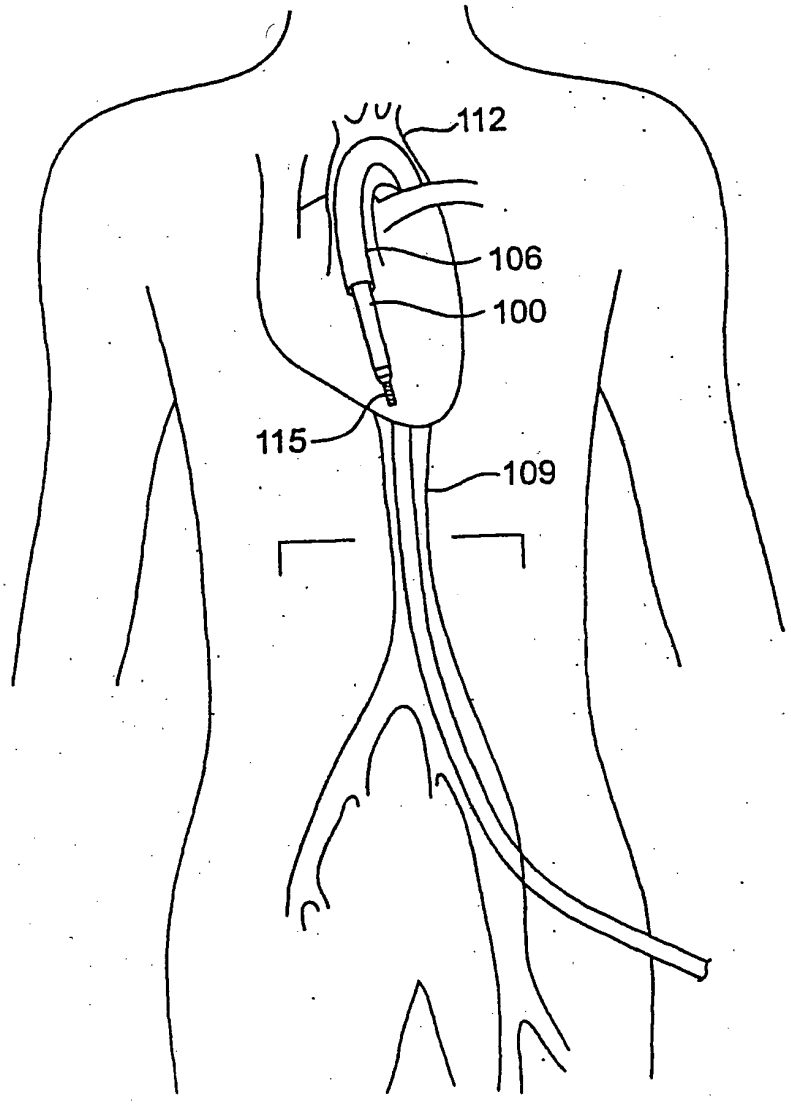

FIG. 6A

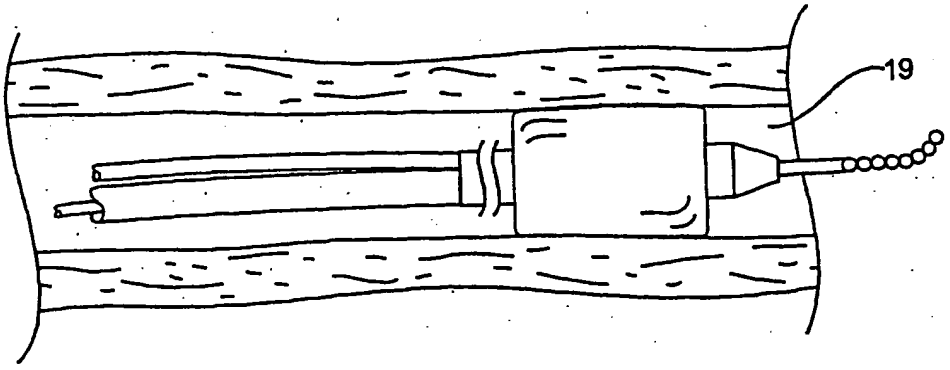

FIG. 6D

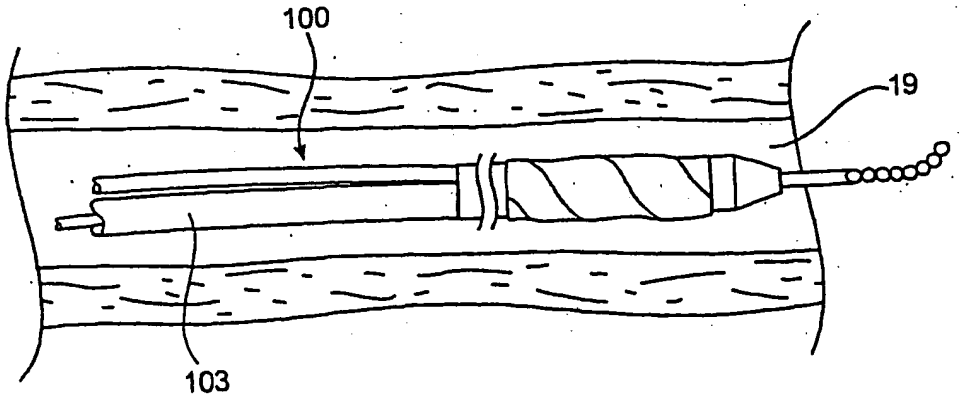

FIG. 6E

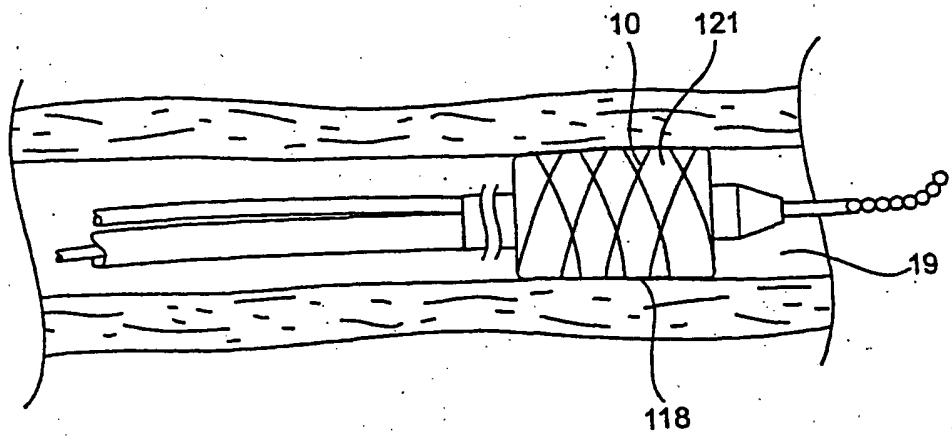

FIG. 6H

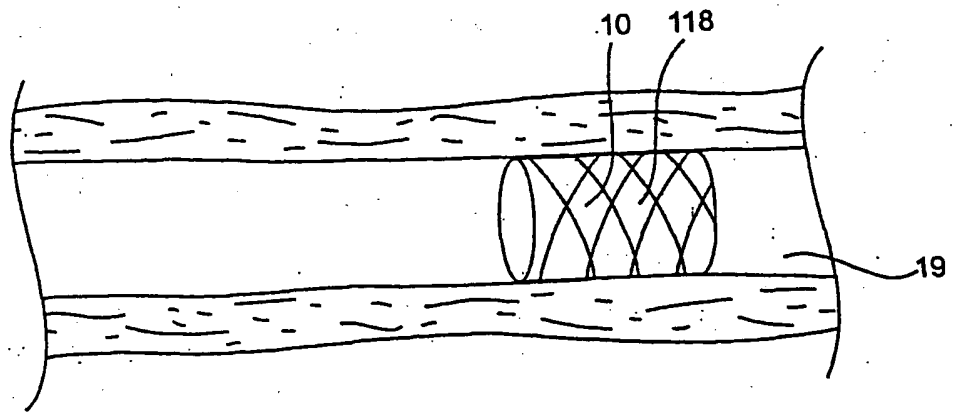

FIG. 6I

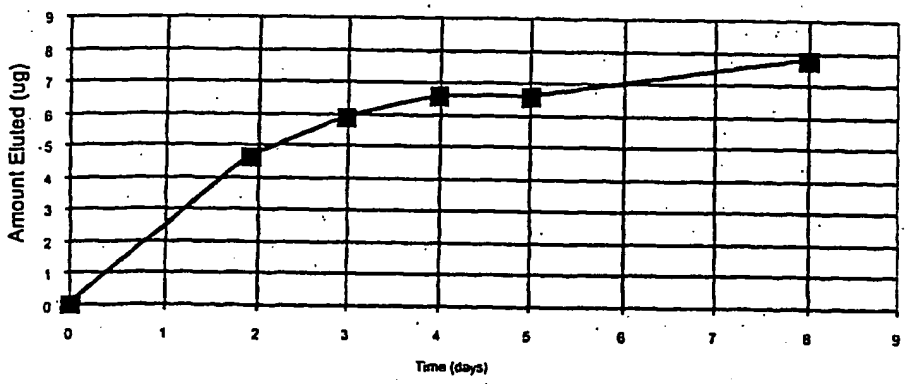
Amount Eluted (ug)
0
1
2
3
4
5
6
7
8
9
Time (days)

FIG. 8A

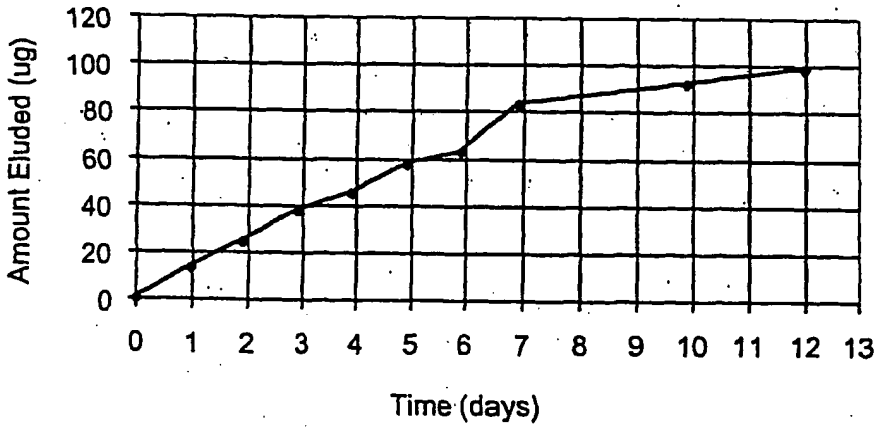
Amount Eluded (ug)
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Time (days)

FIG. 8B

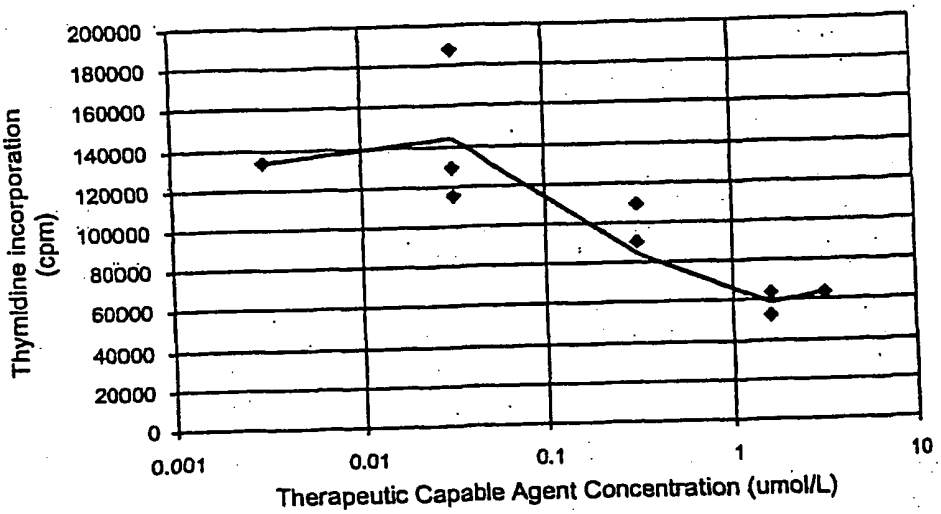
Thymidine incorporation (cpm)
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
0.001
0.01
0.1
1
10
Therapeutic Capable Agent Concentration (umol/L)

FIG. 9C

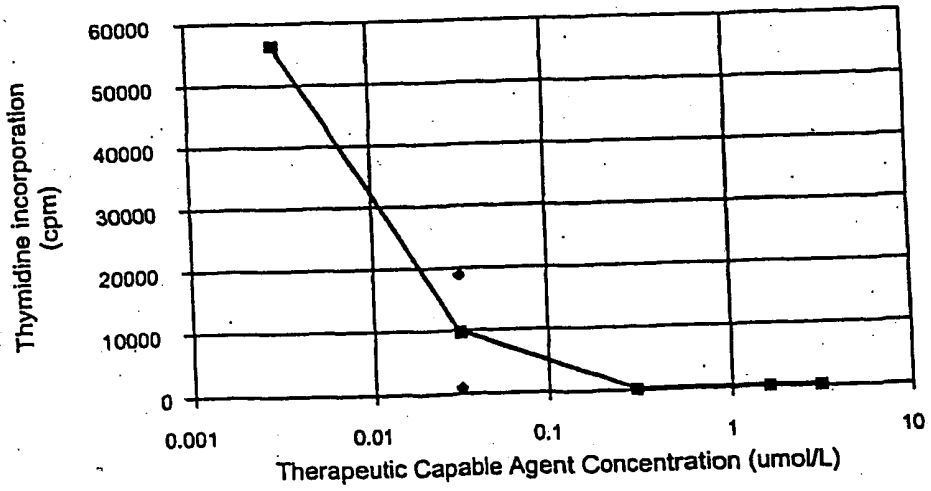
Thymidine incorporation (cpm)
60000
50000
40000
30000
20000
10000
0
0.001
0.01
0.1
1
10
Therapeutic Capable Agent Concentration (umol/L)

FIG. 9D

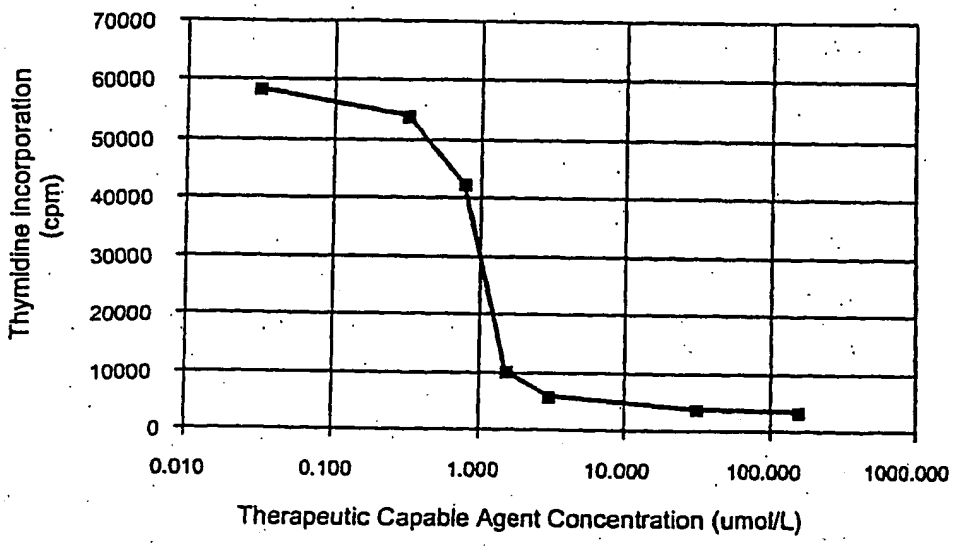

FIG. 10A

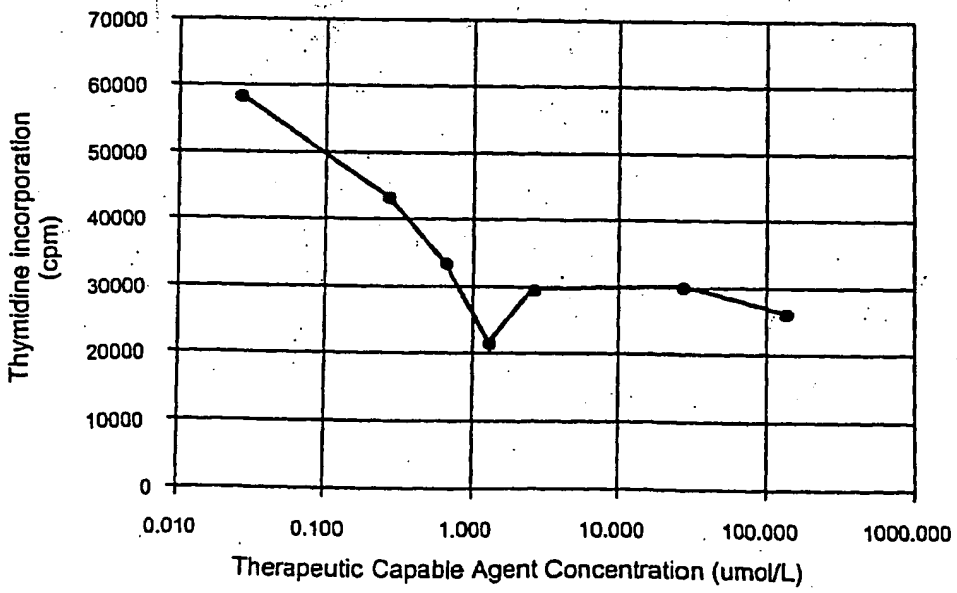

FIG. 10B

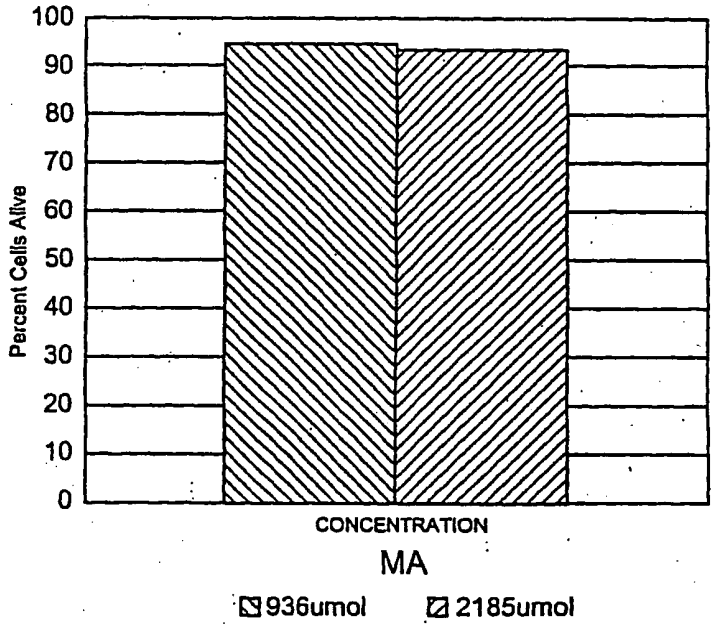
100
90
80
70
60
50
40
30
20
10
0
Percent Cells Alive
CONCENTRATION
MA
936umol
2185umol

FIG. 11B